ACUTE TOXICITY SUMMARY

ETHYLENE GLYCOL MONOBUTYL ETHER

(2-butoxyethanol, butyl cellosolve, butyl glycol)

CAS Registry Number: 111-76-2

I. Acute Toxicity Summary (for a 1-hour exposure)

Inhalation reference exposure level	**14,000 µg/m³**
Critical effect(s)	irritation
Hazard Index target(s)	Respiratory System

II. Physical and Chemical Properties (HSDB, 1994 except as noted)

Description	colorless liquid
Molecular formula	$C_6H_{14}O_2$
Molecular weight	118.20
Density	0.90 g/cm^3 @ 20°C
Boiling point	171°C
Melting point	-70°C
Vapor pressure	0.76 mm Hg @ 20°C
Flashpoint	unknown
Explosive limits	unknown
Solubility	soluble in water, acetone, benzene, carbon tetrachloride, ethyl ether; miscible with ketones, ethers, alcohols and halogenated hydrocarbons
Odor threshold	0.10 ppm (geometric mean) (AIHA, 1989)
Odor description	sweet, ester-like, musty (AIHA, 1989)
Metabolites	butoxyacetic acid (Johanson *et al*., 1986)
Conversion factor	1 ppm = 4.84 mg/m³ @ 25°C

III. Major Uses or Sources

Ethylene glycol monobutyl ether (EGBE) is used as a coupling agent to stabilize immiscible ingredients in metal cleaners, textile lubricants, and cutting oils (HSDB, 1994). It is also used as a solvent for nitrocellulose resins, spray lacquers, enamels, and varnish removers. EGBE is also found in hydraulic fluids.

IV. Acute Toxicity to Humans

Two adult male volunteers were exposed to 113 ppm (550 mg/m³) EGBE for 4 hours. Eye, nose and throat irritation, taste disturbances, and headache and nausea were reported (Carpenter *et al.*, 1956). Erythrocyte osmotic fragility and urinalysis were normal in the subjects during and after exposure. In this study, 8-hour exposures at the same concentrations resulted in similar reports of discomfort.

Four volunteers were exposed either mouth-only or skin-only, by a mouthpiece or a respirator in a chamber, to 50 ppm EGBE for 2 hours (Johanson and Boman, 1991). Capillary blood samples were taken at regular intervals to determine rate of uptake from dermal and inhalation (mouth-only) exposure. The experiment was done under both normal and raised humidity conditions. The authors concluded that dermal uptake of EGBE from air is approximately four times greater than respiratory uptake. The authors also note that dermal uptake increased with air temperature and humidity.

Seven healthy male adults were exposed to 20 ppm (100 mg/m³) EGBE in a chamber experiment designed to assess pulmonary uptake and metabolism of EGBE. Butoxyacetic acid was the primary metabolite found in the urine (Johanson *et al.*, 1986). The authors report that 57% of the inhaled dose was absorbed in the respiratory tract. The authors report that none of the subjects complained or showed any adverse effects from exposure for 2 hours to 20 ppm EGBE.

Although increased erythrocyte fragility has been observed in rodents following exposure to EGBE (Carpenter *et al.*, 1956), recent studies found no increase in the fragility of human erythrocytes taken from normal and susceptible individuals (persons with hereditary spherocytosis or sickle cell disease and older persons) following a 4-hour incubation with butoxyacetic acid (Udden, 1994; Udden and Patton, 1994).

Predisposing Conditions for EGBE Toxicity

Medical: Persons with preexisting neurological, blood or kidney conditions might be more sensitive (Reprotext, 1999).

Chemical: Unknown

V. Acute Toxicity to Laboratory Animals

A 7-hour LC_{50} for mice was reported as 700 ppm (3,000 mg/m³) EGBE (Werner *et al.*, 1943). Severe hemoglobinuria was observed; hepatic focal necrosis and splenic lymphoid hyperplasia were noted at necropsy. An 8-hour LC_{50} in rats was reported as 564 ppm (2,800 mg/m³) EGBE (Pozzani *et al.*, 1959).

No mortality or other clinical signs of toxicity were observed in 5 male and 5 female guinea pigs exposed to 691 or 633 ppm EGBE, respectively, for one hour (Nachreiner, 1994). Further, no signs of toxicity were observed during the 14-day post-exposure period or at necropsy.

Rats were exposed to 867, 523, or 202 ppm EGBE for four hours (Dodd *et al*., 1983). Exposure was lethal to all animals in the 867 ppm group and to 2/6 males and 3/6 females in the 523 ppm group. No deaths were observed in the 202 ppm EGBE exposure group. Rats exposed to 867 ppm exhibited loss of coordination and shallow breathing and had a red discharge around the urogenital area. Red-stained fluid in the urinary bladder and enlarged and discolored kidneys were observed at necropsy of the animals that died during or following exposure to 867 or 523 ppm EGBE.

Increased erythrocyte fragility was observed in rats exposed for 4 hours to 62 ppm (300 mg/m^3) EGBE (Carpenter *et al*., 1956). No significant increase in erythrocyte fragility was observed following a 4-hour exposure to 32 ppm (150 mg/m^3) EGBE.

Corley *et al*. (1994) developed a physiologically based pharmacokinetic model to describe in rats and humans the disposition of EGBE and its major metabolite, 2-butoxyacetic acid (BAA); BAA is the agent that causes lysis of red blood cells. The model predicted that rats metabolize EGBE and eliminate BAA faster per kg body weight than humans do. The balance of the two processes in addition to physiological differences between species resulted in higher predicted peak blood concentrations for rats as well as total areas under the blood concentration (AUC) time curves for BAA. The species differences in kinetics coupled with the fact that human blood is significantly less susceptible than rat blood (and mouse blood and probably rabbit blood) to the hemolytic effects of BAA (Udden *et al*., 1994a,b) indicate that there is less risk for hemolysis in humans as a result of exposure to EGBE than predicted solely by standard rat toxicity studies.

VI. Reproductive or Developmental Toxicity

No studies on the developmental and reproductive toxicity of EGBE in humans were located in the literature.

Pregnant rats were exposed to 0, 25, 50, 100, or 200 ppm EGBE 6 hours per day on days 6-15 of gestation (Tyl *et al*., 1984). A significant increase in the incidence of delayed skeletal ossification was observed in the offspring of rats exposed to 100 or 200 ppm EGBE. Maternal toxicity, as indicated by decreased body weight gain, decreased food consumption, and significantly decreased erythrocyte indices, was observed in rats exposed to 100 or 200 ppm EGBE. It is not clear whether the reported delayed ossification effects indicate distinct developmental toxicity since there was concurrent maternal toxicity (RCHAS, 1994).

The same study exposed pregnant rabbits to 0, 25, 50, 100, or 200 ppm EGBE 6 hours per day on days 6-18 of gestation. Treatment-related increases in maternal deaths, spontaneous abortions, and decreased body weight were observed in does exposed to 200 ppm EGBE. Embryotoxicity, indicated by reduced gravid uterine weight and a concomitant reduction in total and viable fetuses, was observed at 200 ppm. Hematological parameters in the does were normal. However, rabbit erythrocytes resemble rat erythrocytes and are therefore also sensitive to the hemolytic effects of the reactive metabolite of EGBE (Ghanayem *et al*., 1992). The study indicates a LOAEL of 200 ppm and a NOAEL of 100 ppm for maternal and embryotoxicity in

rabbits. EGBE has not been listed as a developmental or reproductive toxicant under Proposition 65.

VII. Derivation of Acute Reference Exposure Level and Other Severity Levels (for a 1-hour exposure)

Reference Exposure Level (protective against mild effects): 14,000 μg/m³

Study	Carpenter *et al*., 1956; Johanson *et al*., 1986
Study population	human volunteers 2 in Carpenter; 7 in Johanson *et al.*)
Exposure method	inhalation of 113 ppm for 4 hours (2 men) in Carpenter *et al.* (1956); inhalation of 20 ppm in Johanson *et al.* (1986)
Critical effects	mucous membrane irritation of the nose and eyes
LOAEL	113 ppm
NOAEL	20 ppm for 2 hours
Exposure duration	2 or 4 hours
Equivalent 1-hour concentration	28 ppm (20^2 * 2 hours = C^2 * 1 hour))
LOAEL uncertainty factor	1
Interspecies uncertainty factor	1
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	10
Reference Exposure Level	2.8 ppm (14 mg/m³; 14,000 μg/m³)

Two human volunteers were exposed to 113 ppm EGBE for 4 hours (Carpenter *et al*., 1956). Symptoms observed included nasal and ocular irritation, disagreeable metallic taste, and a slight increase in nasal mucus discharge. The time to onset of symptoms was not specified; thus no time adjustment was made. Volunteers exposed to 98 ppm for 8 hours with a 30-minute break and 3 volunteers exposed to 195 ppm for 8 hours showed similar symptoms. The 3 exposed to the highest level agreed that it was too high for comfort. In Johansen *et al*. (1986) 7 healthy adults were exposed to 20 ppm in a study designed to look at the toxicokinetics of EGBE. The authors report that the subjects did not complain of adverse effects. Thus, this level can be identified as a freestanding NOAEL.

Level protective against severe adverse effects

No recommendation is made due to the limitations of the database.

Tyl *et al*. (1984) exposed pregnant rabbits to 0, 25, 50, 100, or 200 ppm EGBE 6 hours per day on days 6-18 of gestation. Treatment-related increases in maternal deaths, spontaneous abortions, and decreased body weight were observed in does exposed to 200 ppm EGBE. Embryotoxicity, indicated by reduced gravid uterine weight and a concomitant reduction in total and viable fetuses, was observed at 200 ppm. The study indicates a LOAEL of 200 ppm and a NOAEL of 100 ppm for maternal and embryotoxicity in rabbits. Rabbit erythrocytes resemble rat erythrocytes and are therefore also sensitive to the hemolytic effects of the reactive metabolite of

EGBE (Ghanayem *et al*., 1992). Hematologic parameters in the does were normal but there was evidence in their cages of hematuria. Therefore, it is not clear if the reproductive and fetal toxicity were secondary to hematological effects. No adverse effects to does or fetuses were observed following exposure to 0, 25, 50 or 100 ppm EGBE. This study indicates a LOAEL of 200 ppm and a NOAEL of 100 ppm for maternal toxicity and embryotoxicity in rabbits. The pharmacokinetic model of Corley *et al*. (1994), as well as other evidence in humans and incubated human erythrocytes, indicates that that there is considerably less risk for hemolysis in humans as a result of exposure to EGBE than predicted solely by standard animal toxicity studies.

Level Protective Against Life-threatening Effects

No recommendation is made due to the limitations of the database.

Data on lethal effects of EGBE in species resistant to the hemolytic effects of EGBE were not available other than a 1-hour free-standing NOAEL of 633-691 ppm in guinea pigs (5 per sex) (Nachreiner, 1994). The only lethality study providing dose-response data had been conducted in mice (Werner *et al., 1*943). Both rats and mice have been shown to be sensitive to hemolysis following EGBE exposure. This effect is not observed in humans, including sensitive human subpopulations such as the elderly or those persons with sickle cell disease or hereditary spherocytosis (Udden and Patton, 1994; Udden, 1994). Therefore, the use of mouse lethality data may not accurately reflect the risk of potentially lethal effects in humans following EGBE exposure.

VIII. References

(AIHA) American Industrial Hygiene Association. Odor thresholds for chemicals with established occupational health standards. Akron (OH): AIHA; 1989. p. 14

Carpenter CP, Pozzani UC, Weil CS, Nair JH, Keck GA, Smyth HF Jr. The toxicity of butyl cellosolve solvent. Arch Ind Health 1956;14:114-131.

Corley RA, Bormett GA, Ghanayem BI. Physiologically based pharmacokinetics of 2-butoxyethanol and its major metabolite, 2-butoxyacetic acid, in rats and humans.Toxicol Appl Pharmacol 1994;129(1):61-79

Crump KS and Co, Inc. Probit (Log-Normal) software for the IBM-PC. Ruston (LA); 1983.

Crump KS. A new method for determining allowable daily intakes. Fundam Appl Toxicol 1984;4:854-871.

Dodd DE, Snellings WM, Maronpot RR, Ballantyne B. Ethylene glycol monobutyl ether: Acute, 9-day, and 90-day vapor inhalation studies in Fischer 344 rats. Toxicol Appl Pharmacol 1983;68:405-414.

Ghanayem BI, Ward S, Wall C. Effects of 1-butoxyethanol (BE) and its toxic metabolite, 2-butoxyacetic acid (BAA) on blood from various mammals in vivo and in vitro [abstract]. Toxicologist 1992;12, 282.

(HSDB) Hazardous Substances Data Bank. National Library of Medicine, Bethesda (MD) (CD-ROM Version). Denver (CO): Micromedex, Inc.; 1994. (Edition expires 4/30/94).

Johanson G, Boman A. Percutaneous absorption of 2-butoxyethanol vapour in human subjects. Br J Ind Med 1991;48:788-792.

Johanson G, Kronborg H, Naslund PH, Nordquist MB. Toxicokinetics of inhaled 2-butoxyethanol (ethylene glycol monobutyl ether) in man. Scand J Work Environ Health 1986;12:594-602.

Nachreiner DJ. Ethylene glycol butyl ether: Acute vapor inhalation toxicity study in guinea pigs. Project ID 94N1392. Export (PA):Bushy Run Research Center (BRRC), Union Carbide Corporation; 1994. Sponsored by the Chemical Manufacturers Association, Washington (DC).

Pozzani UC, Weil CS, Carpenter CP. The toxicological basis of threshold limit values: 5. The experimental inhalation of vapor mixtures by rats, with notes upon the relationship between single dose inhalation and single dose oral data. Ind Hyg Assoc (no volume #) 1959:364-369.

(RCHAS) Reproductive and Cancer Hazard Assessment Section. Memorandum on ethylene glycol monobutyl ether reproductive toxicity to George Alexeeff, Air Toxicology and Epidemiology Section (ATES) from Jim Donald, Reproductive Toxicology Unit. July 20, 1994.

Reprotext ® System. Dabney BJ, editor. Denver (CO): Micromedex, Inc.; 1999. (Edition expires 1/31/1999).

Tyl RW, Millicovsky G, Dodd DE, Pritts IM, France KA, Fischer LC. Teratologic evaluation of ethylene glycol monobutyl ether in Fischer 344 rats and New Zealand white rabbits following inhalation exposure. Environ Health Perspect 1984;57:47-68.

Udden MM. Hemolysis and deformability of erythrocytes exposed to butoxyacetic acid, a metabolite of 2-butoxyethanol: II. Resistance in red blood cells from humans with potential susceptibility. J Appl Toxicol 1994;14(2):97-102.

Udden MM, Patton CS. Hemolysis and deformability of erythrocytes exposed to butoxyacetic acid, a metabolite of 2-butoxyethanol: I. Sensitivity in rats and resistance in normal humans. J Appl Toxicol 1994;14(2):91-96.

Werner HW, Mitchell JL, Miller JW, Von Oettingen WF. The acute toxicity of vapors of several monoalkyl ethers of ethylene glycol. J Ind Hyg Toxicol 1943;25:157-163.